TED ROGERS CENTRE
FOR HEART RESEARCH

DONOR STEWARDSHIP REPORT

April 2020 – March 2021

Presented May 2022

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Presidents' Message



Dr. Ronald Cohn



Dr. Kevin Smith



Professor Meric Gertler

This year's annual report marks a pivotal moment in the history of the Ted Rogers Centre for Heart Research, and an excellent opportunity to reflect on the Centre's many accomplishments.

It is an impressive list.

Since 2014, the Centre has reduced rehospitalizations for heart failure by 50 per cent with the proprietary patient monitoring technology Medly; reduced admissions to hospital from the emergency department with a novel heart failure risk score algorithm; provided patients with individualized genetic profiles to provide targeted treatments; seeded innovative startups in heart failure treatment and care; and much more. We hope you will enjoy reading details of these achievements in the following pages.

This year, thanks to a remarkable new $90-million investment from the Rogers Foundation, the Centre is set to continue and significantly expand this work.

This new phase – "Rogers 2.0" – will sustain the Centre's work in perpetuity and will bring the promise of precision health to patients across Canada and around the world. Precision health treats each person according to their unique genetic, structural, and environmental profile to better diagnose, correct, predict, and prevent heart failure. As the world continues to face unprecedented pressure amid the COVID-19 pandemic, this model of remote, personalized care will prove vital in relieving some of the immense pressure on our health-care systems.

This would not have been possible without the extraordinary vision and generosity of the Rogers family in bringing together leading experts across three world-class Canadian institutions in the Ted Rogers Centre for Heart Research. On behalf of The Hospital for Sick Children, University Health Network, and the University of Toronto, we would like to thank you for your continued support, which will help people with heart failure across Canada and the world live longer, healthier lives.



Dr. Ronald Cohn
President and CEO,
The Hospital for Sick Children



Dr. Kevin Smith
President and CEO,
University Health Network



Professor Meric Gertler
President,
University of Toronto

Year-6 at the Ted Rogers Centre

from Executive Director Dr. Mansoor Husain

Year-6 marks a period of momentum and change at the Ted Rogers Centre for Heart Research as our now six-year-old collaborative institute transitioned into our second half-decade. In this report, we provide a contextualized look at efforts spanning our programs, which includes a retrospective on how far we've come, key highlights along the journey, and a look ahead to the results of signature projects underway now.

One key storyline at our Centre has been our ability to accelerate out of a pandemic, rather than stay mired inside of one. Our programs and investments did not slow as COVID-19 continued throughout Year-6, and in fact we ramped up efforts in ways that demonstrated how unique and essential the Ted Rogers Centre has proven to become.

CENTRE TAKES A TECHNOLOGY-DRIVEN LENS

Notably, our investments in digital health innovations and remote patient management rose swiftly to the forefront. Through our Medly program, UHN clinicians remotely onboarded 500 new patients during COVID – a tremendous scale needed for the Heart Function Clinic team to provide virtual care and keep vulnerable patients safe and out of the hospital. Medly meant that heart failure patients could be managed from afar despite the deep health-care crisis. Another app was built, called RCOVID, through which clinicians conducted more than 23,000 virtual visits and tracked and triaged at-risk patients – an innovation UHN acknowledged as one of its most important developments of 2020/21. RCOVID was born from our hallmark Digital Cardiovascular Health Platform, whose data environment and analytical potential has been the foundation of a hospital-wide digital health initiative.

Technology is at the heart of our "Transform HF" initiative, born in Year-6 solely from the Ted Rogers Centre, led by two of our scientific leads, Dr. Heather Ross and Craig Simmons. This new collaboration unites heart failure clinicians, tech innovators, data and AI experts, patients, Indigenous health experts and more in conceiving and creating new ways to bring quality cardiovascular care and treatments to all Canadian communities. Through Transform HF, we will translate new innovations, led by microtechnologies, biosensors and artificial intelligence, and create new ways to keep patients with heart failure safe and empowered while enabling proactive – rather than reactive – clinical care.

That same proactive lens is at the base of our precision medicine efforts guided by scientific leads at SickKids. Using whole genome sequencing, we are increasingly having direct impacts on the medical management of children and adults with heart failure, at the same time as we hunt for genomic clues to cardiac disease. And collaborative innovations are in practice here and around the world – such as the PRIMaCY risk prediction tool led by Dr. Seema Mital that predicts sudden cardiac death in children with hypertrophic cardiomyopathy and can guide their personalized care. It is available online for any physician to use, and is now supported by the American Heart Association.

INNOVATION AND KNOWLEDGE TRANSLATION

Meanwhile in Year-6, our Centre's COVID-related Innovation Fund projects have begun to bear fruit. One, led by Dr. Vlad Dzavik, focuses on whether key diabetes treatment already proven to benefit the heart can protect COVID-19 patients from future heart damage. It earned CIHR funding, and a multi-national trial investigating this new therapy is underway in Canada and beyond. Another, led by Dr. Jay Udell, takes aim at predicting which COVID patients are at risk of adverse outcomes because of specific risk factors. Its goal is to identify the co-morbidities, clinical factors and treatments most commonly associated with cardiovascular complications of COVID.

In our ongoing efforts to share knowledge and inspire cardiovascular researchers, our first virtual symposium landed in December 2020, attracting more than twice as many participants as our in-person conferences had. Recently, this past December, we reprised this popular event with a second virtual symposium that again drew a great response and again comprised a day devoted to research and a day devoted to managing and preventing heart failure in primary care. Across both virtual events we've been able to engage more than 1,000 unique participants.

TRAINING AND PROPELLING YOUNG RESEARCHERS

In Year-6, our team took even more concerted efforts to engage young and emerging heart failure researchers within Toronto and beyond. To that end we planned our inaugural Trainee Day, which was held in early Year-7. We invited a small committee of clinical and basic science trainees to help strategize this half-day event, which included: a session on how to use biobanks to enable translational research; a career workshop led by four former trainees with new positions in industry and academia; and a poster session where participants presented their projects to researchers and clinicians. This event drew more than 100 participants, and was overseen by our brand new Martha Rogers Chair in Heart Failure Training & Education, Dr. Michael McDonald.

Through the pandemic we were able to continue funding novel ideas from trainees through our annual Education Fund competition that we have successfully held each year beginning in 2015. Many of these awardees have been spurred by our funding to achieve new heights, including two who created companies based on their innovations that each earned $250,000 in startup funding through our externally-judged ECHO Pitch competition.

Across health care, it's been a relentlessly challenging time. I am so proud that our teams have risen to new levels of impact right when our expertise was needed most. Looking ahead, we will continue to innovate, to test new ideas that others cannot (for lack of funding), to drive education and knowledge translation, and to press forward with projects whose goal is to have newfound positive impact on the lives of people with (or at risk of) heart failure.

Despite the ongoing pandemic, our teams embrace the mission, forge ahead, and you'll find many of our efforts detailed in this Year-6 report.



Dr. Mansoor Husain
Professor of Medicine, University of Toronto
Executive Director, Ted Rogers Centre for Heart Research

Education Fund Award Recipients – 2020

TRAINEE	PROJECT	SUPERVISOR(S)	INSTITUTION(S)	COLLABORATOR(S)
Post-Doctoral Fellowship (4)				
Rathnakumar Kumaragurubaran (*renewal*)	Epigenetic and metabolic control of diabetes-induced heart failure	Jason Fish	UHN	Michael Wilson, SickKids Paul Delgado-Olguin, SickKids Mansoor Husain, UHN Hai-Ling Margaret Cheng, UofT
Fernando Luis Scolari	Evaluation of clonal hematopoiesis in advanced heart failure	Filio Billia	UHN	John Dick, UHN Sagi Abelson, OICR Gary Bader, UofT Patrick Lawler, UHN
Xingjian Liu	Development of label-free techniques for quantifying conduction velocity and contractility of iPSC-cardiomyocytes	Yu Sun Jason Maynes	UofT SickKids	
Rasha Al-attar	Gene-edited hPSC-CMs as a novel strategy to eliminate graft-related arrhythmias	Michael Laflamme	UHN	Anthony Gramolini, UofT Kumaraswamy Nanthakumar, UHN
PhD (3)				
Tamrat Befekadu*	Real world evaluation of angiotensin receptor-neprilysin inhibitors in heart failure: studies in comparative effectiveness, decision modelling, and economic burden	Harindra Wijeysundera	UofT - SHSC	Heather Ross, UHN Petros Pechlivanoglou, SickKids
Mengyi Song	Dissecting the conserved gene regulatory mechanism underlying the reactivation of the fetal gene program in heart failure	Ian Scott	SickKids	Anthony Gramolini, UofT Michael Wilson, SickKids
Katya D'Costa	Design and validation of a functional small diameter pulmonary artery graft	Paul Santerre	UofT	Christoph Haller, SickKids

TRAINEE	PROJECT	SUPERVISOR(S)	INSTITUTION(S)	COLLABORATOR(S)
Top Up (PhD, 5)**				
Erika Wang	Organ-on-a-chip model of angiotensin II-induced cardiomyopathy for pre-clinical drug testing	Milica Radisic	UofT	Anthony Gramolini, UofT Andew Emili, Boston U
Rysa Zaman (*renewal*)	A novel cardioprotective role of type I interferon in hypertensive heart disease	Slava Epelman	UHN	Boris Hinz, UofT Tania Watts, UofT
Xavier Lee	Role of the alpha-11 integrin in right ventricular heart failure	Kim Connelly	UofT - SMH	Mark Friedberg, SickKids Chris McCulloch, UofT
Homaira Hamidzada	Development of human embryonic stem cell-derived cardiac macrophages for cardiac regeneration	Slava Epelman	UHN	Gordon Keller, UHN Michael Laflamme, UHN Milica Radisic, UofT
Jaykumar Patel	MRI-guided respiratory motion correction for catheter-based therapy delivery in myocardial infarction	Graham Wright	UofT - SHSC	Nilesh Ghugre, SHSC Hai-Ling Margaret Cheng, UofT Michael Laflamme, UHN

* Deferred

** External award recipient provided with top up funding



Integrated Program for Excellence in Heart Function

YEAR-6: MILESTONES

YEAR	MILESTONE	STATUS
4-10	Work with medical device and smart appliance manufacturers and communications technology providers to establish the first heart function home monitoring platform in the world	Ongoing
4-10	With this technology, patients' heart rate and rhythm, blood pressure, weight, salt and caloric intake and compliance with medications will be continuously monitored	Ongoing
4-10	Hand-held devices with external electrical contact plates will allow a physician to remotely see a patient's ECG. With automated analysis tools, the patient's hand-held device will tell them if they have an abnormal heart rhythm.	Ongoing
4-10	Develop new monitoring devices and software in collaboration with Ted Rogers Centre partners at TBEP	Ongoing
4-10	Development and assessment of this tech to be supported by experts in human factors design and health technology assessment at both IBBME and UHN	On track
3-10	Implement the routine measurement of Patient Reported Outcome Measures (PROMS) in ambulatory heart failure care and heart transplant	On track
4-10	Establish and implement home IV inotrope protocol	Ongoing
4-10	Early diagnosis via analysis of "omics" data sets	Ongoing
3-10	Ongoing operation of the biobank to support programming activities, including the collection, storage and processing of patient samples – including next generation gene sequencing and whole gene analysis	Ongoing
4-10	Capital investment to create a customized digital cardiovascular health platform at the Peter Munk Cardiac Centre	Ongoing
2-10	Ongoing activities to support research via computational biology & clinical mobility	Ongoing
5	Assemble and integrate molecular and clinical data emerging from Ted Rogers Centre, in collaboration with the Ted Rogers Chairs in Cardiac Genetics and Heart Function Biology, to inform the personalization of cancer, cardiac, and other therapies in patients with or at risk of developing heart disease	Ongoing

YEAR	MILESTONE	STATUS
3-5	Work with the Ted Rogers Chair in Cardiac Tissue and Cellular Systems Modelling to test how drug toxicities detected in the clinical program can be prevented in patient-specific cardiac tissue constructs.	Delayed (no chair in place)
5	Hold first international conference on the relationship between non-cardiac drug therapies and abnormalities of the heart.	Delayed (to 2022 due to COVID)

THE STORY UNTIL NOW...

The Ted Rogers Centre for Heart Research Integrated Program for Excellence in Heart Function comprises many coordinated efforts designed to revolutionize the ways we deliver heart failure care, optimize outcomes, and use emerging data science and analytics to bolster patient care and perform groundbreaking research.

Consisting of the Comprehensive Program in Heart Function, the Cardiovascular Biobank, the Cardiotoxicity Prevention Program and the Ted Rogers Computational Biomedicine and Clinical Utility Program, this Integrated Program is supported by an array of cardiologists, data scientists, scientists, technology innovators, heart failure nurse professors, and other collaborators.

Our program has grown and proven exceptionally impactful in the past half-decade, and its members and innovations are in high demand for breakthrough research that is truly pushing the field forward. All efforts are guided not only by investigators but by a cadre of research associates and coordinators that ensure the continuity and success of clinical trials, no matter how complex.

THE RISE OF MEDLY: A GAME-CHANGING REMOTE HF PROGRAM

One of the most significant developments at the Ted Rogers Centre is "Medly" – a unique, effective remote heart failure management program. Medly has grown exponentially to become standard of care at UHN, transforming the experience for patients, their families and the health-care team.

With the Medly app, patients at home record their weight, blood pressure, heart rate and any symptoms they are feeling. (With heart failure, even small fluctuations can be dangerous.) Based on individual parameters set by cardiologists, an expert rules-based algorithm filters that information in real time and immediately messages the patient. For example: everything is okay, keep following your care plan; you need to visit emergency; we need to adjust medication.

Meanwhile, the system alerts the health-care team back at Peter Munk Cardiac Centre if a patient's status is deteriorating. In this way, Medly keeps patients safe at home, guarded by specialized care they would otherwise need to access through regular system channels. Medly enables one clinician to provide comprehensive care to more than 250 patients – far beyond standard telemonitoring rates of 75 patients.

AN INNOVATION WITH VAST POTENTIAL

The vast potential of this innovation is coming into focus. In 2020, Health Canada designated Medly as a Class II medical device – the first for any telemonitoring system. Our study that year proved Medly reduced rehospitalizations for heart failure by 50 per cent, a key goal of the Ted Rogers Centre. It also reduced all-cause admissions by 24 per cent, while improving patient self-care and quality of life.

Medly proved extremely valuable as COVID-19 emerged. Our teams remotely onboarded 500 new patients during the pandemic – thus allowing these vulnerable patients to avoid a hospital trip. Medly was a prime tool by which the Heart Function Clinic team could efficiently provide virtual care to patients in their homes.

Medly is proven to safely up-titrate guideline-directed medical therapy faster than typical care, getting patients to target doses of medications with fewer visits. This further distinguishes Medly as a cost-effective method to keep patients safe away from the hospital.

Medly is also spreading well beyond UHN. Agreements are in place to deploy Medly in five Ontario specialty cardiac centres (Sunnybrook, Women's College Hospital, St. Michael's Hospital, Sinai Health and Markham Stouffville Hospital)

and primary care settings (Mamaway Wiidokdaadwin Primary Care Team and Family Health Teams in Couchiching and Alliston). To facilitate this expansion, we're working with Ontario Health Teams to further operationalize Medly outside of UHN as it is increasingly viewed as a key provincial asset. It is formally endorsed by CorHealth, Ontario's cardiac, stroke and vascular care agency.

Medly also fuels new research projects, leading to 15 peer-reviewed publications, half of which involve external partnerships.

Enhancements to Medly continue apace with efforts to expand its reach. We have used artificial intelligence (AI) approaches to elevate its algorithm even more, adding EMR data and other elements in a way we proved can improve its accuracy without compromising safety. We are currently working on an expert rules system to allow automatic titration of guideline directed care, a world first.

DIGITAL HEALTH AND PREDICTIVE ANALYTICS

Our digital health innovations caught the eye of Apple, which partnered with our team to test how Apple Watches and iPhones can improve our ability to monitor heart failure patients. The newest and most exciting project is the Ted Rogers Understanding Exacerbations in Heart Failure (TRUE-HF) study. While there were slowdowns due to COVID, it's ramping up and we performed an analysis of the first 50 participants in fall 2021.

Our team's strengths truly came together in response to the pandemic. As we recognized the looming effects of the shutdown on our patients and model of care, we drew on our hallmark project – the Digital Cardiovascular Health Platform (DCHP) – and married its sophisticated computational and analytical environment with clinical insights to create the "RCOVID" app.

RCOVID is lauded as one of UHN's most important initiatives in 2020-21, helping clinicians efficiently deliver virtual care and track and triage at-risk patients, and leading to a steep decline in emergency department admissions. In the first year using RCOVID, clinicians performed 23,464 visits, vastly improving efficiency without reducing access to care.

Here's how it works: RCOVID pulls data from the DCHP and prepopulates fields for physicians using it. This information is accessible all in a single pane for them to see – bloodwork, COVID tests, all interactions with the health-care system. By the time a virtual visit is finished, all fields are completed in synaptic format – and with the push of a button, clinicians can transform it into a traditional clinic note that gets stored in the EMR and accessible to all doctors in the patient's circle of care.

EXECUTING A VISION FOR BIG DATA

Such data-driven integration and optimization solutions create more efficient clinical care while also enhancing data integration, because of the synaptic capture, into the DCHP "data lake." Through this sophisticated infrastructure we can discover, integrate, store and share data on all cardiovascular patients at UHN, with four key goals:

- Enhance patient care (quality improvement, safety, outcomes)
- Enable systems biology levels of clinical and basic science discovery (by integrating data from millions of patient encounters, real-world evidence, and clinical trials)
- Drive the use of predictive analytics
- Serve as architecture for new real-time digital health platforms.

The Integrated Program's Big Data vision flows from the DCHP and draws on the analytical excellence of the Ted Rogers Computational Program in data science, machine learning and traditional statistical methods to drive both care and research into the future. It allowed us to unlock siloed, un-linkable, and even previously discarded data. It enabled clinical teams to perform advanced analytics into risk analysis (causes), prognosis and treatment of HF (via biostatistics, machine learning, and AI). And it enabled investigators at UHN and SickKids to study heart failure from new angles – with ~200 data analytics projects underway at the end of Year-6.

The DCHP's innovative data environment and vision has proven so valuable that it inspired UHN's new technology-focused research mission and is the foundation for a hospital-wide Digital Health Platform.

The Integrated Program's analytics are extraordinary and industry-leading – with teams able to perform complex analyses with advanced machine learning techniques. Many signature studies are published, and soon to be published, including a manuscript on if and how weather

conditions influence heart failure outcomes. Another led to a model that predicts worsening heart failure based on the raw "breath-by-breath" data captured by a cardiopulmonary exercise machine. For the cardiotoxicity program, this team is supporting a clinical trial studying how exercise therapy can be used to improve heart health of childhood and adolescent cancer survivors.

AN IN-DEMAND BIOREPOSITORY FOR RESEARCH

The effort by the Peter Munk Cardiac Centre to build a cardiovascular biobank started in 2012, but it wasn't until the Ted Rogers Centre's commitment that this endeavor took off. Our biobank has grown significantly to become a key resource in empowering translational research within and beyond our Centre. More than 90 per cent of biobank expenditures flow directly to collaborations with various principal investigators who have groundbreaking ideas to explore.

Our team has consented 17,000 patients to the biobank, which now stores more than 275,000 of their samples. This grows by about 50,000 each year, far exceeding initial expectations. Our biobank now enrols patients from 12 clinics across UHN, with ICUs and inpatients as the next step.

We've had considerable interest in the biobank within the Ted Rogers Centre and Peter Munk Cardiac Centre, and are also receiving queries from external scientists in Ontario and beyond. (To date, samples from 30 per cent of consented patients have been released.) This reflects the recognized strengths of our biobank with the breadth of biospecimens and the depth of clinical annotation via the DCHP. Importantly, we are one of the first biobanks registered with the Research Ethics Board. It also meets Canadian certifications, with an oversight committee staffed by experts in various disciplines who can judge the quality and validity of any proposed study.

The biobank is now used as a service for a wide variety of clinical trials. One pivotal project is an international collaboration called SODIUM-HF (site PI: Dr. Heather Ross), now complete, which aims to be the definitive trial on understanding if a low-salt diet leads to fewer clinical events and better outcomes for patients. It leverages our biobank and our expertise, as Peter Munk Cardiac Centre was the top recruiting centre in the world, bringing 160 patients to this 800-patient study.

Another international collaboration focuses on cardiogenic shock, for which the biobank stores specimens. Because of this, we are the only Canadian site asked to join an international registry, leveraging the digital platform in place that seeks to predict which patients will have worse outcomes based on biomarkers, genetics and extensive clinical data.

The biobank can't receive direct funding from CIHR or Heart & Stroke so, without Ted Rogers Centre support, its rich resources simply wouldn't exist to fuel research.

A WORLD-RENOWNED CARDIOTOXICITY PROGRAM

Our Program in Cardiotoxicity Prevention is the largest in Canada, caring for patients at risk for, or with cardiovascular complications from cancer therapy. By studying how it develops, and through early detection, prevention and long-term care, the program supports cancer patients in receiving the most optimal cancer therapy while ensuring that they aren't left with yet another life threatening problem – heart failure.

Since inception, the clinical program has grown by more than 500 per cent and now serves 2,000 patients each year at the Peter Munk Cardiac Centre. Lengthening waitlists demonstrate the demand and growing recognition among patients and clinicians (e.g. oncologists) of the unique service provided. A new full-time nurse practitioner and clinical fellows supported by the Ted Rogers Centre have improved our ability to provide timely care – and another dedicated clinician will soon be needed to meet the rising demand.

The program has had direct impacts on patient outcomes. For example, amongst women with breast cancer receiving cancer therapy that puts them at high cardiovascular risk, incidence of heart failure has decreased by ~50 per cent in our clinic compared to historical rates at the Princess Margaret Cancer Centre. We have added unique new services, such as the clonal hematopoiesis clinic that cares for patients with genetic mutations in blood cells that predisposes them to both cancer and heart disease. It is the first such clinic in Canada and one of the first globally.

Research is a major highlight of the cardiotoxicity program. The team conducts prospective and retrospective studies and clinical trials focused on recognizing and preventing heart disease in cancer patients. These studies have promoted multicenter international collaborations and

global leadership in the field enabled by the diverse team gathered within the program enabling efficient conduct of research studies.

The resources within the program have also enabled investigators to obtain large peer reviewed grants to support specific ongoing research projects.

Notably, the Centre provided the financial ability to hire research coordinators, who are key to positioning our program as major players in global studies. For example, in the landmark SUCCOUR trial that compared imaging strategies to detect heart failure in cancer patients, our site recruited the most patients out of 26 sites around the world. We recruited twice as many patients as the next highest centre – hugely significant for a randomized trial. Now, researchers look to our cardiotoxicity program and our site to support major international trials.

WORLD-LEADING RESEARCH

The program has produced one of the largest volume of impactful new knowledge compared to any other individual academic center globally. Many studies in recent years have provided unique new information in a rapidly evolving field. Dr. Thavendiranathan published four studies using provincial data that demonstrated the actual rate and consequence of cardiotoxicity in patients with cancer treated in Ontario. Published in high-impact journals, these findings have helped shape patient care globally. Also, this work has led Dr. Thavendiranathan to receive the first-ever Canada Research Chair in Cardio-oncology, which will enable the team to pursue broader fields of research.

Dr. Abdel-Qadir, another cardiologist in the program, developed the world's first risk prediction model to identify patients with breast cancer at risk for heart disease five and 10 years in the future. This was a major contribution to the field as it now enables clinicians to recognize patients at the highest risk of cardiotoxicity even before cancer therapy begins. In 2021, Dr. Abdel-Qadir published the largest study in the field examining cardiac arrhythmias in patients with bone marrow cancers receiving targeted cancer therapy. This study provided unique data on risk factors for arrhythmias and potential treatment strategies. Through his expansive work, Dr. Abdel-Qadir earned the prestigious Canadian Cardiovascular Society's Young Investigator Award in 2021.

Overall, the Ted Rogers Program in Cardiotoxicity Prevention has had a major role in advancing the cardiovascular care of patients with cancer locally, nationally, and internationally. The program is recognized internationally as evident from the number of lectures provided but our faculty at major scientific conferences, the contribution to clinical practice guidelines and international scientific positions statements, and the request by cardiologists globally to train within the program.

LOOKING AHEAD...

As we look ahead to the next few years, there are major pushes across the Integrated Program for Excellence in Heart Function driven by diverse collaborators.

Our teams are leaders in their disciplines and, as assets and capacity become more and more integrated with the rise of data, it will bear both intended and unexpected benefits. Our reach will expand within our partner institutions and far beyond the province, the country, and indeed internationally.

We have the potential with digital tools such as Medly to create a new standard of care for heart failure, increase access by extending it across Ontario in a foundational way. Through our expertise in biobanking and cardiotoxicity, we can continue to make widespread impact both in Canada and globally.

Inside our program, care efforts led by Ted Rogers nurse practitioners will continue to drive virtual titrations and optimize guidelines-directed therapy to heart failure patients without the need to visit the hospital. This effort that, led to a standalone titration clinic in Year-6, is part of a mission to ensure high-quality, accessible care is provided to patients anywhere.

There will be a substantial push to expand our pillar of digital health and predictive algorithms – a cornerstone of where heart failure care must go. Collaborations with other sites are well underway, as well as directly with Ted Rogers Centre programs at UofT (TRANSFORM HF) and SickKids (hypertrophic cardiomyopathy efforts).

Our Martha Rogers Chair in Heart Failure Training & Education, held by Dr. Michael McDonald, will pursue innovation and academic excellence in training the next generation of clinical fellows in heart failure. This includes recruiting top global candidates who are eager to join Canada's only formal cardio-oncology program. We will search for more opportunities to translate knowledge and

drive guidelines and evidence into practice – while also delivering a new educational portal for patients in spring 2022 via a revamped website.

We will strengthen our engagement of policymakers, bringing the best of our clinical and research expertise together to inform policy, education and health systems in Ontario and beyond.

Our cardiotoxicity prevention program will shift into actionable next steps, asking: how can we take what we've learned and prevent heart problems in patients? We have a model to predict the risk of heart issues in breast cancer survivors – how can we now use preventative therapies in these patients as well as fast-track those clinically who are at higher-risk? How can we use what we know about clonal hematopoiesis to prevent heart disease in patients?

Meanwhile, our team is set to uncover the evidence-driven approach to using a new cardio-oncology rehabilitation program (with funds from the Canadian Cancer Society and CIHR) to improve patient outcomes, an effort to be led by a kinesiology expert hired through Ted Rogers Centre funding.

Cardiac Precision Medicine Program

YEAR-6: MILESTONES

YEAR	MILESTONE	STATUS
1-10	Next-generation sequencing based diagnostics	Ongoing
1-9	Functional validation using hiPSC models	Ongoing
2-8	Tissue studies: Expression profiling of myocardium to study the molecular signaling pathways of heart failure	Ongoing
1-10	Cardiac biobanking	Ongoing
3-10	Genetic- and pharmacogenetic-guided therapies	Ongoing
1-10	Cardiac phenotyping and genotype-phenotype associations	Ongoing
6-10	Pilot clinical trials of new genetic-guided therapies	Delayed (due to COVID)

THE STORY UNTIL NOW...

One in 100 children is born with a structural heart defect. Others are born with defects in heart muscles. While surgery works to cure some defects, other young patients go on to develop heart failure. In the absence of effective treatments, 50 per cent of children require a heart transplant or die within five years of a heart failure diagnosis.

Understanding the genetic basis of childhood-onset heart failure is one of the first steps to develop medicines that target the underlying cause. The Cardiac Precision Medicine Program leverages the power of sequencing to unravel the unique genome of every child with heart disease and heart failure and drive a precision medicine approach to their care.

Through research discoveries made as part of the Ted Rogers Centre, we are able to tailor the prevention and treatment of heart failure in children and families based on their unique genetic and biological profile as well as environmental and lifestyle choices.

In six years, our program has made significant strides in understanding what causes heart disease in children and finding better ways to prevent complications, provide timely therapy, and improve outcomes. This is made possible through a state-of-the-art biobank, next-generation sequencing technologies, big data and AI supported analytics, multidisciplinary collaborations, exciting international partnerships across four continents, and close partnership with our patients. This type of translational program is truly unique in the world.

AMONG THE WORLD'S LARGEST PEDIATRIC BIOBANKS

Our genomics research is made possible thanks to patient participation in the Heart Centre Biobank, funded by the Ted Rogers Centre, one of the largest international biorepositories for childhood onset heart disease in the world (and Canada's largest). The biobank has more than 10,000 participants of all ages, spanning children and adults, and involves multiple sites across Ontario, Canada and beyond.

The biobank provides researchers and clinicians access to vital genetic samples and data – an invaluable resource for studying the genetic and environmental causes of heart failure, individualizing care, and developing new treatments. Samples from nearly half of participants have

now been accessed for more than 50 studies locally, nationally and internationally.

WHOLE GENOME SEQUENCING EFFORTS TAKE OFF

Our program uses whole genome sequencing to decode the missing causes of heart disease in children as well as machine learning methods to create tools that predict risk of a child developing heart failure and other complications. We are one of the first research programs to find hidden clues to heart disease in the "non-coding" genome.

Through Year-6, our team performed genome sequencing on more than 300 families with cardiomyopathies from our biobank. This work involved a strong collaboration with Genomics England, which enabled us to identify the genetic cause in twice as many families as with conventional genetic testing.

Our team also completed genome sequencing in more than 1,200 children and adults born with cyanotic congenital heart disease. This includes the two most common causes babies being born blue: tetralogy of Fallot (TOF) and transposition of the great arteries (TGA). Our project was selected for funding by ERAPerMed in 2019, an ERA-Net CoFund supported by 23 countries and co-funded by the European Commission. This transatlantic effort involves partners from Germany and the Netherlands and has led to exciting new genetic discoveries that explain many of these heart defects. These findings are being returned to families, benefitting patients from all these participating countries.

A NEW BIOINFORMATICS DISCOVERY PIPELINE TAKES SHAPE

Analyzing a person's genome requires advanced bio-informatics to find the few rare disease-causing variants from amongst millions of variants in our genomes. Bioinformatics is a discipline that blends computer science with biology to analyze and interpret biological data – in our case, genomic data.

Our bioinformatics team applies advanced analytics and AI methods to compare genomes from our patients with those of hundreds of thousands of healthy individuals. The goal: to find hidden clues about the genetic causes of heart disease. This "pipeline" can save genome analysts precious time and generate results much faster than relying on manual methods. We are offering it to collaborators around the world.

IMPORTANT RECENT ADVANCES

Targeting precision medicines for genetic cardiomyopathy

Myosin is a protein required for the heart to contract and pump. Gene defects in myosin are the leading genetic cause of cardiomyopathies. Leveraging a Ted Rogers Centre strategic innovation grant, a subsequent CIHR grant, and bioengineering collaborations at the University of Toronto (TBEP), Dr. Seema Mital and James Ellis at SickKids generated beating heart cells from reprogrammed skin and blood cells from healthy individuals and from patients with cardiomyopathy in our biobank.

These induced pluripotent stem cells (iPSCs) are some of the highest-quality iPSCs bringing precision to the study of a wide variety of diseases, including heart failure. CRISPR gene editing was able to correct the gene defect and rescue the heart failure phenotype in the dish.

The team also showed that a drug that targets the myosin protein also reduces the thickening of these heart muscle cells in children with hypertrophic cardiomyopathy. While the drug has been tested in adults, we now look forward to pediatric trials of these targeted drugs that have the potential to help young children with severe disease and no available treatments.

Using pharmacogenetics to choose the right drug

We know that a person's genetic make-up drives how they metabolize drugs and whether they respond to the drug. Through pharmacogenetics we are able to detect each person's likely response to a medication and the risk for side effects in their genetic profiles.

Pharmacogenetic testing of children with heart failure who were on a ventricular assist device and waiting for a heart transplant helped us identify if the blood thinner they needed was likely to work or not. We were thus able to choose the right blood thinner in order to reduce the risk of blood clots and stroke.

This is precision care at its best – the right drug, for the right patient, at the right time.

A calculator that saves lives

One of the hallmark achievements in our Cardiac Precision Medicine Program is "PRIMaCY," the world's first validated risk prediction tool to predict sudden cardiac death in children with hypertrophic cardiomyopathy.

In a collaboration with 22 centres across Canada, the United States and Australia using data from several hundred patients, we developed and validated this risk calculator that blends clinical, imaging, physiological and genetic factors on each patient to create an individualized risk prediction for sudden death.

The study was published in 2019 in *Circulation* and has had a global reach. The online tool is now available as a web application that can be accessed by physicians anywhere in the world.

Through better understanding of each patient's risk, clinicians can engage in informed shared decision making discussions with affected patients and families, to guide the use of devices like implantable defibrillators that can prevent sudden death.

This approach to individualized risk stratification was supported by the 2020 American Heart Association/ American College of Cardiology guidelines for diagnosis and treatment of hypertrophic cardiomyopathy was co-chaired by Dr. Seema Mital, scientific lead of the Cardiac Precision Medicine Program.

Blood biomarkers for early diagnosis of hard-to-detect diseases

Dr. Robert Hamilton at SickKids made two deeply impactful discoveries in the past three years that bring new hope for people at risk of two lesser-studied heart conditions that can cause sudden cardiac death.

In 2018, he published a study in the *European Heart Journal* documenting an incredible finding: one specific antibody, anti-desmoglein-2, was found in every patient who had arrhythmogenic cardiomyopathy (ACM) This is leading to the development of a new – and simple – blood test that could accurately identify up to 95 per cent of patients with ACM, before they show any symptoms. (In contract, genetic testing identifies about 35 per cent – thus missing the majority of cases.)

In 2020, he again published a study in the *European Heart Journal* that is paving the way to change how Brugada syndrome is diagnosed. This rare condition affects about 18,000 Canadians, but nine in 10 people have no diagnosis – instead, the first sign they have the condition is because they died from it. That's because electrocardiograms and genetic testing are not sensitive enough to spot this disease. Here, they found a new biomarker, a protein, that was implicated. With global collaborators, they then proved that a simple blood test was 100 per cent sensitive in diagnosing Brugada syndrome.

Using AI to predict cardiotoxicity in children who survive cancer

Our team used machine learning to identify childhood cancer survivors who are at risk of developing cardiotoxicity from anthracyclines, a common class of cancer therapy drugs.

We recruited more than 1,000 patients to this study involving centres in Canada and the U.S., of whom nearly 300 underwent exome sequencing. From here, our team combined clinical and genetic risk factors to build a machine learning model to help predict who is likely to develop heart damage after being treated with anthracyclines. In so doing, we also found new genetic targets for medications that could protect the heart.

Genetics and AI can therefore help not only children with genetic heart conditions but also children with cancer by identifying those at risk for cardiac side effects before being exposed to the drug. Physicians can then use this information to modify cancer therapy to reduce a child's risk of such side effects.

New hope for infants waiting for a heart transplant

One-third of infants with end-stage heart failure die before they can receive a heart transplant due to organ shortage. Dr. Osami Honjo, a cardiac surgeon at SickKids, developed the only *ex vivo* (outside the body) cardiac perfusion system that can resuscitate and repair pediatric hearts from both marginal and donation after circulatory death (DCD) donors. Doing so could enable them to be transplanted into infants and young children on the waiting list.

This unique system, once proven in a clinical trial, is expected to increase the number of usable donor hearts for this vulnerable population and enable them to survive to transplant.

Engaging and empowering families in health care

An important goal of our research is to make our genetic findings available to help patients and families in real time. To accomplish this, in partnership with the Cardiac Genome Clinic, we communicate new and actionable findings back to the patients and families so that they are able to make informed decisions about family screening and family planning.

Through Year-6, we had communicated 70 novel findings. This helped in ending the diagnostic odyssey for these families, by helping them understand what caused the heart disease, helping in recurrence risk counselling and screening other family members for heart disease, and importantly, helping them better cope with the diagnosis.

Our study describing best practices on how to return genetic findings from research to families was published in *BMC Medical Genomics* demonstrating leadership in disseminating our knowledge to help other programs around the world implement these best practices.

Training the next generation

We are leading best practices in clinical care and in training the next generation. Besides developing clinical practice guidelines, Dr. Seema Mital became the first female editor of the 10th edition of the *Moss and Adams' Heart Disease in Infants, Children and Adolescents*, the definitive textbook for pediatric cardiology. Our program involves education in heart failure for clinical and research trainees, and education days for patients, siblings and families to improve their understanding of their heart condition and to empower them in self-managed care.

LOOKING AHEAD...

Our Cardiac Precision Medicine Program continues to offer promising opportunities for clinical translation, commercialization and knowledge dissemination to the broader scientific community and public.

Looking ahead our aim is to build on the research discoveries and advance toward widespread clinical impact. We aim to:

- Translate genomic and biomarker-based diagnostics into clinical tests
- Conduct first in-child clinical trials of new genetic guided therapies
- Implement precision analytics as decision support tools embedded in electronic health records
- Implement individualized drug dosing in health information systems
- Deploy new technologies such as our Ex Vivo Organ Perfusion Systems, wearable technologies for remote monitoring, and AI-driven algorithms for bedside early warning systems.
- Create universal consenting to enable every child with heart disease to be enrolled into our biobank and link genetic, clinical and physiological data in electronic health records.

Creating a unique biological and digital footprint for each child will help us track their trajectory, identify early warning signals of worsening heart failure and intervene before complications occur. Dr. Aamir Jeewa at SickKids is working closely with Ted Rogers Centre scientific leads Dr. Heather Ross (exploring the use of Medly in children) and Craig Simmons (exploring the use of smart textiles) to integrate digital health technologies into remote monitoring of pediatric heart failure patients. Remote monitoring can facilitate closer monitoring, and timely management as outpatients, thereby reducing hospitalizations while keeping them safe at home.

Looking ahead, we will continue to work towards applying precision health to change patient lives for the better. We will accomplish this through an equal partnership with our young patients, honoring the principle of "nothing about us without us."

Cardiac Genome Clinic

YEAR-6: MILESTONES

YEAR	MILESTONE	STATUS
2-6	Recruit 100 families per year through Cardiac Genome Clinic	On track
2-7	Whole genome sequencing (WGS) for identified priority families	On track
2-5	Ethical implications of genetic testing in cardiac care	On track
3-7	Health economics of genetics in heart disease	On track
4-7	Pilot clinical trials of new genetic-guided therapies	On track

THE STORY UNTIL NOW...

Precision medicine means tailoring therapy and care for an individual person – rather than by using data gathered around similar patients. To that end, the Cardiac Genome Clinic uses whole genome sequencing (WGS) to identify the genetic cause of heart failure that helps optimize care for patients and family members while generating potential individualized treatment options.

For a child with congenital heart disease where all clinical genetic testing options have been exhausted, WGS opens a vast new door to a possible diagnosis. It helps families plan for the future (e.g. reproductive options, genetic testing for pregnancies) and proactively determine if other specialists should be seen. Results can provide new answers to families about the roots of their loved one's condition, and inform care, follow-up, and whether other family members should be screened for heart problems.

Since receiving Research Ethics Board approval in fall 2016, the Cardiac Genome Clinic has grown into a recognized and respected program to advance the use of WGS in the cardiology clinic. It is one of Canada's only such programs, and in fact one of the world's only genomic clinics to span children and adults, courtesy of the Ted Rogers Centre's two partner hospitals.

EXPANDING BASE OF FAMILIES AS PARTNERS IN RESEARCH

Our program relies on the participation of families willing to join this genomic project during often difficult, sensitive times. They understand, with the support of our genetic counsellor, that there is the opportunity to find answers for their family members, and also contribute to important research in a field set to be hugely important in coming years and decades.

In most cases we enrol not only the "proband" (the first person in the family who is affected by heart disease – at SickKids, this is a child) but parents and affected relatives as well. As of the end of Year-6 (April 2021) we had consented 405 families, enrolling 355 enrolled at SickKids, 51 at UHN, and our first two families from Mount Sinai Hospital's Prenatal Diagnosis and Medical Genetics Program.

This Mount Sinai expansion means that our program now spans across prenatal, pediatric, and adult care. This newer prenatal focus is valuable for many reasons. Recent literature shows that up to 15 per cent of fetuses with cardiac defects or system anomalies have a genetic cause that is possible to identify. As it stands, fetal congenital heart disease testing

includes autopsy and microarray genetic testing – a limited scope that misses many genetic diagnoses.

With this limited (and, critically, no developmental) information, it is difficult to select a targeted gene panel for further testing. Comprehensive genome-wide sequencing helps overcome this challenge – which is why our team is leading efforts to use WGS prenatally. A genetic diagnosis for fetal CHD helps families to understand the risk for disease recurrence and enables reproductive options. Ultimately, understanding the etiology of congenital heart disease is the first step toward achieving precision medicine and care.

SEQUENCING & RETURNING RESULTS

Our team performed WGS on 38 new families in Year-6, bringing the total number of families sequenced to 274 (as of April 2021).

Key to our work is returning clinically actionable findings to patients. Our team returned 77 unique findings to families during Year-6 – led by 10 actionable primary findings for children at SickKids. There were also actionable secondary findings discovered in two SickKids families, which impacted their medical management.

One example of the impact of these results comes recently from a family new to the program. In deploying WGS, we identified a never-before-seen variant of uncertain significance within a well-known clinical gene. Previous clinical testing in this patient failed to detect the variant because of technology limitations.

While more studies will have to look at this suspicious variant, the result will likely lead to a genetic diagnosis for the family that, in turn, informs their care, informs recurrence risk and family planning, and will lead to cascade testing and screening for other family members.

In another example, we found a gene variant related to vascular Ehlers Danlos syndrome – a condition that requires multi-disciplinary care to screen for and proactively manage secondary complications. This diagnosis could have life-saving implications since its first sign in those not known to be at risk is often a life-threatening blood vessel or organ rupture.

In another example, we found a pathogenic variant in a gene related to a Lynch syndrome, a hereditary condition that puts people at high risk of colorectal and endometrial cancer. This genetic diagnosis enabled the family to proactively begin colorectal screening and undergo prophylactic surgery to reduce cancer risk.

TAILORING THE RIGHT TREATMENTS TO EACH PATIENT

One strong program focus that makes a direct patient impact is in pharmacogenomics (PGx). This testing, in which we hunt for drug-gene pairs, is a powerful new tool to select the best medications and doses to ensure the safety and wellbeing of patients, and improve their outcomes.

Monitoring the safety and effectiveness of medications in children is profoundly important, particularly in clinics that deal with complex medical conditions such as heart failure requiring many different drugs.

At our Cardiac Genome Clinic, we've seen that clinical PGx testing regularly impacts treatment plans in children with heart disease. For instance, a young patient may metabolize warfarin too quickly, meaning that this drug may thin their blood too quickly – a dangerous condition if left unchecked. In Year-6, we validated PGx results in 77 families, bringing the total (as of April 2021) to 122 families with clinically validated, significant PGx findings.

In May 2021, our team published a milestone paper that demonstrates our leadership in this important area. It assessed how PGx testing could be used clinically in a complex pediatric setting – something that is not yet done well. The goal was to help overcome a challenge in this field: to integrate PGx testing into real-time care and use it to make decisions on each patient.

Led by Iris Cohn, the collaborative team studied 172 children and targeted six genes known to be key in PGx. They found that, for 37 per cent of these young patients, the targeted medications treatment they were taking should in fact change – because their genotype was incompatible with those drugs. They also found that 80 per cent of the patients would be recommended to receive non-standard treatments based on their PGx profiles.

In short, this "multiplex" testing program led to recommendations that differed from standard treatments. This means that, by using this approach, we can provide more tailored heart medications to children – ones more likely to work, and less likely to cause adverse effects. The findings indicate that PGx data has real-world value, and is helping

advance the application and understanding of such data in routine pediatric care.

A REVOLUTIONARY NEW BIOINFORMATICS TOOL

One major advance in this program is the development of "GeneTerpret" – a bioinformatics tool that professionals can use to assess whole genome and whole exome sequencing data and be able to better identify genetic variants that are causing disease. For the good of the field, which works in unison to comb through the vast genome searching for the underpinnings of disease, we made the tool available for all at Geneterpret.com.

What happens is a genetic analyst uploads data to GeneTerpret, and then filters the information by using many integrated databases and modules. The result: a priority list of the highest-potential genes or variants that are disease-causing in that particular patient.

GeneTerpret overcomes a pressing problem in this research: the time it takes to analyze a sample. It is a labor and time intensive procedure. An analyst must use various databases to collect information and then merge it with the patient's clinical history as well as what other studies have reported. At the same time, analyzing a genome is a subjective field, and it's hard to standardize a system for all circumstances. But our new tool semi-automates this process and makes it more efficient to interpret a genome – with greater ease and accuracy.

GeneTerpret has the potential to save analysts hours on each case – meaning they can spend far more time hunting for new disease-related genes. A study describing this tool and its achievements is being prepared for publication.

LOOKING AHEAD...

Our team is expanding the reach of this clinic through new collaborations. There are plans to collaborate with another research study that is collecting neurodevelopmental data and outcomes on cardiac patients. The goal will be to combine genetic data with their outcomes to better understand the genomic risk factors for neurodevelopmental problems in the cardiac-disease population.

In Year-6, we were granted REB approval to collaborate with UHN's Techna Institute scientists in an effort to apply artificial intelligence and machine learning approaches to our genotype and phenotype data to enable novel gene discovery. With powerful new algorithms in place, it can expedite genome analysis and provide us insights into untangling the gene-phenotype relationship in heart failure far beyond what is available now.

There is a collaboration with UHN's Dr. Maral Ouzounian to sequence the genomes of patients with aortopathy (dilated aorta, aortic aneurysms). This will be part of a "multi-omics" approach to identify the genetic etiologies of aortic disease, using WGS, transcriptomics and proteomics.

There is a collaboration with Dr. Rachel Vanderlaan (SickKids) to analyze genomic sequences of young patients with pulmonary valve stenosis – an effort to find novel gene candidates. And there are collaborations in a similar vein with SickKids senior scientists Michael Wilson and Ian Scott to focus on left-side lesions on the heart.

The team is also at work building on our novel findings that were first published in 2018 regarding the "vascular endothelial growth factor" (VEGF) pathway, identified for the first time to play an important role in the heart's formation. We initially found that the genetic code for proteins in the VEGF pathway was strongly implicated in adult patients with tetralogy of Fallot.

Now, we are doubling down on this major finding to learn more of the target genes by sequencing unaffected family members of people with the variant. Thus far, seven Cardiac Genome Clinic families have agreed to join the VEGF analysis, allowing us to test 19 additional family members. Knowledge in this new area will yield widespread impact on the management of tetralogy of Fallot, which represents about 10 per cent of all cases of congenital heart disease.

SPECIAL HIGHLIGHT

Introducing TRANSFORM HF: Digital innovation for heart failure care

In Year-6, a new partnership launched between the Ted Rogers Centre and the University of Toronto to reimagine how high-quality, digital approaches to heart failure can be equitably delivered to all people living in Canada.

TRANSFORM HF will enable patients to become more active in their own health and increase equitable access to specialized cardiac care by uniting a multidisciplinary, multi-sectoral team of experts in co-creating innovative technologies as well as proactive, personalized, and decentralized models of heart failure care.

Today, new therapies are dramatically improving quality of life and survival in heart failure, and technology is capable of changing how the disease is managed.

"Unfortunately, these therapies and approaches are underutilized and inaccessible to a lot of Canadians," says Ted Rogers Centre scientific lead Dr. Heather Ross. "Our goal is to unite the right people in devising new medical and artificial intelligence technologies that will achieve equitable access to high-level care across our country's vast geography."

She and fellow scientific lead Craig Simmons (TBEP) are co-leading TRANSFORM HF.

"We will bring together the vast amount of technology developed at the University of Toronto and deploy it in new ways," Prof. Simmons says.

He says that some of these innovations, like biosensors and remote monitoring tools, already exist – and others will be co-designed by experts in different fields, and by patients themselves.

PATIENTS AS PARTNERS

Any innovation is only as valuable as it is practical. For this reason, patients are critical partners of TRANSFORM HF. "In medicine we must do things *with* patients, not *to* patients," Dr. Ross says. "They are the ones who will use these technologies, and they can tell us if our ideas make sense, or how they can be tweaked."

Brad Pope, one of Dr. Ross's patients at Peter Munk Cardiac Centre, is an early patient participant in TRANSFORM HF. "Technology is fantastic and it's helping someone like me achieve my goal of getting back to as close to normal as possible," Brad says. "But we always have to ensure that we have the end user "me" in mind in developing better care and having them at the table from the very beginning." A key goal of the program is to build user-centered technology that can be adapted by any patient, in any environment, with any specific need.

"Our engineers and scientists will help our clinical partners deliver expert care to remote locations and perform continuous monitoring to keep people with heart failure safe."

Craig Simmons, Co-Lead
TRANSFORM HF

"Technology is often developed in a bubble, so for our engineers and scientists to collaborate with patients on design will change everything," Prof. Simmons says. "The ability to interact with end users early will help us create solutions that work more quickly and more smoothly."

MANAGING PATIENTS BEYOND THEIR 'EPISODES OF CARE'

Heart failure is a 24/7 disease, slight changes in clinical status can cause serious problems. The challenge is that we need new methods to monitor patients outside their episodes of care in order to intervene quickly.

The TRANSFORM HF team will devise a new era of biosensors that can be packaged and used by Canadians in any community. These include wearable sensors built into fabric – socks, patches, vests – that monitor clinically relevant vitals like heart rate, blood pressure, breathing patterns and fluid accumulation. They may include a mobile app whose special camera can assess blood flow below the skin, and tech that syncs with consumer products like the Apple Watch.

Prof. Simmons says the team will also conceive new ways of bringing diagnostics that are done in the lab (ex. blood, saliva, urine) to people's homes. "Patients often have to travel for them and wait days for results," he says. "What if we could give them a small device that, for instance, takes a pin prick of blood, runs a test, and produces results in 15 minutes? These microtechnologies already exist, but they haven't been engineered to specifically focus on markers important for heart failure."

Innovations like these can yield oceans of data, which may hold new signals that reveal the state of someone's heart failure or the risk of it worsening. The machine learning component of TRANSFORM HF is about creating algorithms that can predict someone's risk of hospitalization, and enabling clinicians to intervene early to help keep that person in a stable condition.

Because technology is changing so fast, we also need to conceive of new ways to study whether novel technologies work, how we integrate them into virtual care and whether they influence patient outcomes. TRANSFORM-HF teams will design new trials capable of seeing if a sensor works as intended, in the near term. "Because if we wait years to see if our innovations actually work, by then, the technology will have changed," Heather says.

"For decades, we've watched heart failure care evolve incrementally. But with all stakeholders working together, we will generate ideas that allow for transformative changes in how we manage this complex disease. Instead of taking steps we can make leaps."

Dr. Heather Ross, Co-Lead
TRANSFORM HF

TRAINING THE NEXT GENERATION OF SCIENTISTS AND CLINICIANS

To make this mission sustainable, graduate students, scientists and clinicians across disciplines must be trained; for instance, a fellow supervised by both a heart failure doctor and a technology developer at the same time. To achieve realistic targets, this training must expand beyond the lab and into communities and homes where innovations are to be used.

"An immersive training experience allows our students to see first-hand what the constraints are, what power is available, what internet connectivity is like and who the people are that they are designing technology for," Prof. Simmons says. "New innovations will be set up to make a true difference in people's lives."

All of this will rely on brand new partnerships with patients and communities – at all stages of development. "This is a special opportunity to co-create and test new inventions in a collaborative sandbox, and I expect it to build into a long-term funding model to create a pipeline of innovations in the heart failure space," Prof. Simmons adds.

LOOKING AHEAD

TRANSFORM HF, which formally launched in February 2021, carries the spirit of the Ted Rogers Centre itself: to not only make bold claims, but to deliver on them. Ideas that seem cutting-edge today will become the norm in five years.

"Our success in moving the field forward will be entirely tied to the community of people who are dedicated to changing the lived experience of heart failure – patients included," Heather says.

TRANSFORM HF: KEY ACCOMPLISHMENTS

Built and maintained a diverse network of 70+ researchers; clinicians; basic, applied, and data scientists; engineers; people with lived experience; Indigenous communities; health technology experts and innovators; cardiovascular organizations; and startups.

Launched a brand new award for trainees in the heart failure space to accelerate new research ideas.

We awarded four collaboration starter grants in Year-6 to projects that demonstrate the scope of TRANSFORM HF's mission.

- A three-day on-the-land program with teachings by Elders and Knowledge Keepers and guided by the land as a teacher exploring Indigenous research methods, colonization, terminology, socio-political context and current issues that Indigenous people face.
- Researching ways to ensure caregivers are integrated in a "Medly Caretown" initiative, and to overcome any gaps in accessing this virtual care tool – particularly older adults, ethnocultural minority community residents, and those with limited English proficiency.
- Collaborative workshops to assess and create a Canadian framework to assess AI-powered technologies as they become more prominent in health care.
- Conducting studies with patient partners to ensure remote monitoring technology is as useful as possible, how it should be designed, and the specific needs it should meet.

Translational Biology and Engineering Program

YEAR-6: MILESTONES

YEAR	MILESTONE	STATUS
10	Establish TBEP Centre for Models of Heart Failure	On track
6	Develop stem cell models of cardiac disease	On track
7	Develop, validate, and commercialize new diagnostics for early detection of heart failure	On track
10	Develop, validate, and commercialize (micro)tissue models	On track
10	Discover mechanisms of cardiovascular fibrosis and treatment strategies	On track
10	Discover mechanisms and treatment strategies for co-morbidities that cause heart failure	On track
10	Develop strategies and enabling technologies for stem cell-based therapy and endogenous heart tissue regeneration	On track
10	Predictably modulate immune activation during heart disease	On track
7	Research program to study immune system activation	On track
10	Endogenous immune system activation	On track
5	Model signaling and genetic networks in cardiac tissues	Behind schedule*
10	Develop predictive models of heart tissue function	Behind schedule**
10	Omic-derived model of heart dysfunction	On track
10	Cardiovascular biology and engineering training program	On track
10	Additional UofT investment in research program	On track
10	Additional UofT investment in MaRS facility	On track
10	Expansion of commercialization activity and partnerships	On track

* Milestone to be redefined and achieved through research program established by new Chair in Cardiovascular Engineering

** Milestone to be redefined and achieved through research program established by new Chair in Cardiovascular Systems Biology (to be hired)

THE STORY UNTIL NOW...

The Translational Biology and Engineering Program (TBEP) is, from inception, a unique initiative that unites basic scientists from the Temerty Faculty of Medicine and engineers from the Faculty of Applied Science and Engineering in what has become a world-class multidisciplinary centre for discovery and innovation in cardiovascular sciences and engineering.

Our team of collaborating investigators and trainees targets the complex genetic, molecular, and cellular physiology that underpins heart failure in pursuit of the most promising strategies to diagnose and treat cardiovascular disease and repair and regenerate heart tissue.

Through clinical partnerships within the Ted Rogers Centre, TBEP drives a translational research and technology development pipeline from discovery to diagnosis to therapy in which ideas, tools, and technologies are accelerated from bench to bedside to help patients sooner.

To that end, in Year-6, our investigators held 66 grants totaling more than $11 million for interdisciplinary research projects that have created new partnerships inside the program (33 per cent of grants) and within the Ted Rogers Centre (44 per cent of grants).

EDUCATIONAL HUB

Members of TBEP have built and nurtured a Cardiovascular Biology and Engineering Training Program, an educational hub that presently integrates 79 trainees (15 postdocs, 44 PhD, 20 MSc) and 17 research staff from nine separate UofT departments.

A testament to this talented group is that in Year-6, these trainees held nearly $960,000 in scholarships and awards and contributed to 38 peer-reviewed publications in high-impact journals. To date, TBEP has fostered the careers of nearly 170 trainees.

TBEP is also a hub for undergraduate students, inspiring them to focus their efforts in the heart failure space. Forty-six top students have participated in our Undergraduate Summer Research Program (USRP) from 2017 through 2021, each training for up to 16 weeks alongside TBEP investigators, contributing to research and attending workshops and seminars.

A FACILITY LIKE NO OTHER

TBEP was a new 26,000 sq-ft space built within one of the world's largest innovation hubs. The facility serves a range of core capabilities: medical imaging and microscopy, animal surgery and physiological monitoring, advanced preclinical models of cardiovascular disease, genomic and proteomic method development and biomarker detection, biomaterial synthesis and characterization including polymer processing and coating, and microfabrication of in vitro diagnostic devices.

In six years, we have acquired specific equipment to advance the research program, foster collaboration and accelerate translation. Many resulting capabilities at TBEP are unique to Canada, with examples including:

Cardiac imaging suite:
In 2019, we acquired a confocal microscope (equipped with four lasers and an incubation chamber) to perform fluorescent imaging of fixed tissue/cells and live cells. In year-6, we added two valuable new systems:

1. A preclinical high-frequency ultrasound and photoacoustic imaging system (Vevo3100) that allows us to observe the structure, function, blood flow dynamics and molecular imaging of cardiovascular diseases in animal models.

2. A preclinical MRI system capable of rodent cardiac imaging in addition to body and neuroimaging with dedicated imaging coils for both mice and rats. It is fully equipped with physiological monitoring tools and the ability to maintain the subject's body temperature.

Mass spectrometry and proteomic suite:
TBEP is equipped with state-of-the-art mass spectrometers, essential supplementary equipment, and a platform to analyze proteins, peptides and other small molecules in closer detail and resolution than was ever possible before. It is the only heart lab in the world with such analytical capabilities.

AN INCUBATOR OF CARDIOVASCULAR INNOVATIONS

In 2018, the Ted Rogers Centre launched the Entrepreneurship for Cardiovascular Health Opportunities (ECHO) program: a 12-month virtual training program engaging cardiovascular innovators from across Canada.

Led by high-calibre entrepreneurial industry, policy, regulatory and clinical experts, ECHO is designed to:

- Provide entrepreneurship training, mentorship, networking and funding opportunities for early ventures in the cardiovascular health sector
- Aid in transferring research innovations and intellectual property from academic and hospital institutions into the economy
- Create more start-ups in the cardiovascular health sector

Through this program at TBEP, ECHO has (as of April 2021) engaged more than 85 mentors and key opinion leaders, held ~100 workshops and seminars on essential entrepreneurship principles, and supported the training of 27 startup companies. Through the ECHO PITCH competition, where five finalists compete at the end of each year in front of a panel of external judges, we have awarded **$500,000** to support three extremely promising innovations:

1. **Paradox Immunotherapeutics:** They have developed a breakthrough immunotherapy for AL cardiac amyloidosis, where the body's own immune system clears dangerous deposits from the heart caused by a disease with no existing treatment.
2. **Arterial Solutions:** They focus on new diagnostics and have developed the first-ever blood test for peripheral arterial disease. This easily accessible test would help physicians, improve patient lives, and save the system considerable funds.
3. **BioSenseTex:** They focus on at home non-invasive monitoring of people with heart failure using smart textiles. Sensors in fabric can quickly measure fluid accumulation, predict the need for hospitalization, and keep people safe at home.

A PARTNER OF INDUSTRY

In six years, TBEP has engaged with over 28 companies in various capacities. CellScale Biomaterials and Roche Diagnostics have licensed TBEP technologies. Aphaia Pharma, Cohesys, Laetech, MetabolIQ, Polumiros, Rheo Biotechnologies and Qanatpharma are all startup companies that emerged out of TBEP labs.

Finally, the following partners have sponsored research and training programs: Atomwise, Bruker, CellScale Biomaterials, Centre for Commercialization of Regenerative Medicine, Echofos Medical, Evasc Medical Systems, Evonik, Fuji Film – VisualSonics, GlaxoSmithKline, Myant, Olympus, Pfizer, Philips, Ripple Therapeutics, Sanofi, Servier, SmartBots, StemCell Technologies, Tissue Regeneration Therapeutics, and Xerox.

IMPORTANT RECENT ADVANCES

Project: Blood flow to the brain in heart failure

One high-potential project has for years focused on the cystic fibrosis transmembrane conductance regulator (CFTR) and its role in blood vessels. Researchers at the Bolz lab found a molecule called S1P that enters cells through the CFTR and constricts blood vessels in response to pressure. While it is key to regulating a healthy flow of blood to the brain, we know in heart failure that S1P levels are too high and over-constrict the blood vessels.

There exists here an opportunity to repurpose existing cystic fibrosis medications and use them in heart failure. The goal is to use these safe, effective therapies to normalize blood flow to the brain in people with heart failure, helping overcome the often serious cognitive symptoms and mental fatigue related to the disease.

The project spans TBEP, UHN and Lund University (Sweden), and is seeded by TBEP grants and propelled by the Ted Rogers Centre ECHO program. A clinical trial is underway to test if a new therapy based on S1P can increase blood flow to the brain in people with heart failure or subarachnoid hemorrhage (bleeding around the brain) – and an earlier study in mouse models in 2019 proved that it could.

Project: Tracking the molecular pathways of heart failure and cardiac fibrosis

Researchers in the Gramolini lab collaborated with labs at UofT, UHN and Boston University in using advanced phosphoproteomics to yield brand new insights into the molecular nature of cardiac fibrosis. The team detected differences in protein signaling networks between healthy and diseased hearts, and created a map of these pathways that reveals where changes occur in diseased hearts (thus becoming targets for therapy).

What is especailly unique is a mouse model, an organ-on-a-chip model (called the "Biowire") and actual human tissue samples were used to study the signaling pathways. In doing so they also discovered a compound that seems to prevent the development of fibrosis.

This notably was the first time phosphoproteomics has ever been used in a heart-on-a-chip model – and it proved the Biowire, created by TBEP partner Milica Radisic, can realistically reflect a patient's actual heart condition.

This important study, published in *Nature Biomedical Engineering*, was made possible by TBEP seed funds and our mass spectrometry facilities.

Recruitment: Our first Chair in Cardiovascular Engineering

In spring 2021 we recruited Daniel Franklin, a rising star in the field of wearable sensors and implantable medical devices, as Ted Rogers Chair in Cardiovascular Engineering. Daniel credited the Ted Rogers Centre's robust partnerships with hospitals, TBEP's multidisciplinary nature, and teams working together in modern facilities with his decision to move to UofT from Chicago.

Daniel – now assistant professor in the Institute of Biomedical Engineering, TBEP principal investigator, and TRANSFORM HF investigator – will help the Centre's mission to design digital technologies for equitable heart failure care no matter where someone lives. To that end, he aims to establish new concepts and devices that measure hemodynamic metrics such as blood pressure, ejection fraction and/or vascular resistance to keep clinicians informed and people with heart failure safe. He knows that these new devices must actually work for patients with complex heart issues in order to be trusted and used by clinicians.

His research program will target:

- Wearable devices for physiological monitoring
- Implantable devices for sensing and stimulation
- Bio-photonic materials and imaging systems

Recently, Daniel came to an agreement with research sponsor AMS, a huge sensor manufacturer. Through this, the Franklin lab gains spectroscopy equipment that is not available on the market yet. He will build them into wearable devices for a host of biomedical applications and, if successful, it will lead to more opportunities with both AMS and other industry players.

LOOKING AHEAD...

Clinical translation is always an underlying goal of TBEP's work, and close collaborations with clinical partners at UHN and SickKids greatly enable the opportunities to do so. TBEP is home to many projects in various stages of translation, but here is a look at two high-potential areas as we look ahead.

1. A revolutionary biomaterials platform

TBEP investigator Paul Santerre and his team developed a nanoparticle platform (patent application filed) from their immunomodulatory biomaterials platform that is being studied as a delivery vehicle into the heart. Examples of its use include:

- Deliver CRISPR-Cas9 to repair the effects of muscular dystrophy on heart tissue (collaborations at TBEP and SickKids).
- Deliver a sustained release of therapies that can help regenerate heart tissue (collaborations with SickKids).
- Deliver peptides to control over-production of vascular smooth muscle cells and to prevent coronary arteries from narrowing (vascular stenosis) or building up with plaque (atherosclerosis). This has received a new Heart and Stroke grant.
- Control fibrosis in engineered heart valve tissue (collaborations with TBEP, SickKids, Queen's University, and Tissue Regeneration Therapeutics).

2. Regenerating hearts using pluripotent stem cells

TBEP investigator Hai-Ling Margaret Cheng is collaborating with labs at UHN, Sunnybrook, SickKids and TBEP on "re-muscularizing" injured hearts with stem cell-derived cardiac muscle (hPSC-CM) grafts. This work, funded in part by Medicine by Design, has the potential to help us restore heart health rather than just manage heart failure.

The project's key goals are to overcome the remaining barriers to translating an hPSC-based therapy for heart failure following heart attacks, and to explore the pressure-overloaded right ventricle as another target for hPSC-CMs. This expert team is poised to initiate a first-in-human clinical trial that tests hPSC-based cardiac cell therapy.

The Cheng lab has developed a "divalent metal transporter" reporter gene as a new way to monitor implanted human cells. Through this MR cell-tracking technology, in combination with advanced imaging, they will be able to see exactly how an hPSC-CM graft heart muscle is functioning in a pig after a heart attack.

There are tremendous **commercialization opportunities** stemming from the labs in TBEP. One is led by investigator and Ted Rogers Centre scientific lead Craig Simmons, who has developed a special medium formulation that advances stem cell-derived cardiomyocyte functional maturity beyond any existing solution. It can do so in many different culture formats, and can be applied in an array of ways in science and industry.

The project leveraged TBEP seed grants and the ECHO program to explore its commercialization potential. There is a now a new spin-off project on using AI algorithms to mature human iPSC-cardiomyocytes. A patent draft is filed, a new startup company is formed (called MetaboIIQ), and agreements are underway with industry partners.

Looking ahead here are some **notable upcoming projects** worth highlighting here in Year-6:

- Investigator Rodrigo Fernandez-Gonzalez is striving to identify the cellular and molecular mechanisms involved in heart development – in particular, how different cytoskeletal networks contribute to the cell movements that generate heart tubes. Ted Rogers Centre scientific lead Dr. Seema Mital (SickKids) has found mutations in the myosin II gene in patients with childhood heart disease (through genome sequencing). The Fernandez-Gonzalez lab created a Drosophila (fruit fly) model of the most common myosin II mutation and are now examining the effects of that mutation in cell behaviours and cytoskeletal dynamics during early heart development. This unique and rare area of study requires considerable multidisciplinary expertise and has the potential to shift the field.

- The Fernandez-Gonzalez lab is also well down the path of developing an AI-based screen for new myosin II inhibitors. The idea is to predict which drugs and compounds could be refashioned as myosin inhibitors, and use living Drosophila embryos to validate the ideas. This is funded by industry partner Atomwise Inc. and also has the potential for translation.

- Investigators Anthony Gramolini and Scott Heximer are co-leading an intriguing study sourcing how fibrosis forms at a cellular level during heart failure. To that end they are examining G-protein signaling in fibrosis in both mouse and human hearts. Collaborations stretch through five TBEP labs, through UHN and through UofT Dentistry. They are leveraging the TBEP proteomics facility and expertise as well as the Peter Munk Cardiac Centre Biobank, also funded by the Ted Rogers Centre.

- Paul Santerre is collaborating with Michelle Bendeck (TBEP), Mark Friedberg (SickKids) and Craig Simmons to develop tissue-engineered vascular grafts using micro-vascular endothelial cells found in human fat. This is important because these cells are difficult to obtain, and being able to derive them from fat – an abundant, accessible, and uniquely dispensable tissue – would change the field of vascular tissue engineering. Their technique that requires little more than a magnet means that fat may now be regarded as a rich source of endothelial cells with which to build blood vessels and ensure they receive adequate oxygen and nutrients needed to survive.

Update: Chair in Immunobioengineering

In 2018, Dr. Slava Epelman was named the inaugural Loretta Rogers Chair in Immuno-Bioengineering. A cardiologist, immunologist and scientist at UHN, he was tasked with translating new discoveries into strategies to stop heart failure and promote cardiac regeneration. The Epelman lab, embedded for three years inside our Translational Biology and Engineering Program space in the MaRS building, has embarked on a series of collaborative, innovative projects possible only through the funding of this chair position and the Centre's infrastructure.

At a high level, Dr. Epelman says his lab has brought much-needed clarity to role of specific immune cells – which are difficult to distinguish – to very prevalent forms of heart failure:

- **Ischemic cardiomyopathy:** A lack of blood supplied to the heart decreases its pumping ability, caused by ischemia (e.g. having a heart attack or blocked arteries).

- **Non-ischemic cardiomyopathy:** All other causes of decreased heart function, most commonly caused by viral infection, drug reactions, inflammation or autoimmune reactions.

Dr. Epelman has developed novel tools and brought new understanding about different immune cells in the heart and how they act in distinct, important ways when someone develops heart failure.

TARGETING SPECIALIZED IMMUNE CELLS IN THE HEART

Two key studies are worth highlighting as it relates to this focus: one in the setting of a heart attack (ischemic) and the other in the setting of high blood pressure (non-ischemic).

In both, the team tagged immune cells called "embryonic macrophages" that are specialized cells present as the heart develops as a fetus yet still present in the adult heart. They then used machine learning techniques to assign certain functions to these cells – and tried to figure out the role of a subset of these immune cells.

As it turns out, these macrophages stopped heart damage from worsening in both ischemic and non-ischemic diseases. But they did so in different ways. In the former, by tagging and following the cells, they found that the macrophages protected a vulnerable area (called the "peri-infarct zone") right around the location of the heart attack. When the team removed the macrophages, those areas of the heart became dysfunctional and heart cells swelled in size.

Conversely, they found that in the presence of high blood pressure (non-ischemic disease), these macrophages reprogrammed themselves and started to increase in number and cause heart cells to grow in size for a positive reason: in order to pump against the pressure of hyper-tension. When they removed the immune cells, the heart couldn't compensate for the pressure – a remarkable finding to consider that an immune cell has such an important non-immune-related function.

These studies have been published in world-leading immunology journals and advanced this emerging field forward. We now know that primitive macrophages provide different support roles in different diseases. In the heart, we can focus on what molecules they are making to support the heart, which can ultimately be repurposed as possible heart failure therapies.

This is the step toward bioengineering new therapies. Key here is to create these macrophages and prove that they can be beneficially used as stem cell therapies – that they can actually grow and graft to the heart, and be accepted into our heart's complex environment.

REPORTING ON MILESTONES

Establish research program to study underpinnings related to immune system activation resulting from regenerative therapies

To this end, one key project has been a collaboration with Milica Radisic (TBEP, UofT) and Gordon Keller (UHN) to incorporate macrophages into unique "organ-on-a-chip" 3D systems. Can engineering tissues with macrophages create heart cells that have greater function? The idea is to add macrophages to strengthen cardiac muscle tissue patches before they are implanted, and ensure they are more effectively integrated into the heart.

Preliminary results are positive, and Dr. Epelman says that macrophages do seem to improve heart tissue function, suggesting a beneficial effect. The core focus here is to design cells and analyze how they interact with other cells in the heart – particularly after an injury like a heart attack.

Both elements, making cells and ensuring they can live in harmony with cells that others have created, is complex and an active area of study.

Including immune cells in the emerging world of stem cell therapy is very novel, but the Epelman lab has helped push the field forward to show that immune cells organize the heart tissue. They in fact may hold the key to making stem cells a realistic mode of heart failure therapy in the near future. The Ted Rogers Centre is the sole source of funding for this important work, as it is high-risk/high-reward and less likely to attract significant external grants.

Strategies for minimizing immune over-reaction

For regenerative medicine to work as intended, it's vital for a person's own immune system not to over-react to therapies that it may treat as a threat.

Dr. Epelman is testing a system that can target blood monocytes – immune cells that enter the heart when there is an injury or change. These monocytes can trigger damaging inflammation. This lab has learned they will change into other cell types when they reach the heart, some that cause inflammation, and others that in fact protect the heart similar to the macrophages described above).

Instead of blocking monocytes, we instead need to guide them to the right place so they can help. The team is busy understanding what turns them into other cells, whether these cells are making choices or whether it's human evolution. When we know, we can uncover how to foster their healing abilities in the heart.

Strategies to control endogenous immune activation and pathology during disease progression

Dr. Epelman has studied neurotransmitters in mice to see if we can learn ways it applies to heart failure. Of interest, he says, the neuro-immune cell interaction seems to be involved in viral infection of the heart. In models they've made, neurotransmitters released by T cells appear to control inflammation in a viral infection.

Determining what genes are expressed in every heart cell

Dr. Epelman is key to a collaborative project that spans SickKids, UHN and UofT (TBEP) that aims to build a single cell map of the heart in health and in disease development. The idea is to understand what each cell type is doing and thinking, analysis that will reveal why abnormalities occur (and what we can do to prevent them).

The group is focused on congenital heart disease and children born with heart defects. On samples from the Ted Rogers Centre-funded biobanks at SickKids and Peter Munk Cardiac Centre, the team is sequencing each cell and reconstructing how cells communicate with each other. It began with sequencing cells from the right ventricular in children at the time of corrective surgery, results that will be compared to adults with heart failure.

From this work we will seek to predict pathways that are activated during the time when baby hearts can actually regenerate themselves, as well as uncover the relationship of cells and pathways to clinical outcomes.

LOOKING AHEAD...

Dr. Epelman and his team will continue to study how COVID-19 impacts the heart using a new hamster model and state-of-the-art equipment. We don't know yet if the coronavirus directly impacts the heart, nor do we know whether cardiovascular risk factors like high blood pressure and coronary artery disease make someone more susceptible to a worse infection. The heart is one of many organ systems that can be adversely affected by COVID-19.

Moving ahead, this chair will take a purposefully complex lens to decode the complex biological systems involved in preventing or developing heart failure. It is a "systems biology" lens that goes beyond the immediate dimension to give a greater picture – for example, our eyes might see a 2D square when in fact it is a 3D cube. The systems biology lens can see the cube, and that is how Dr. Epelman will lay the foundation so we can deploy regenerative strategies that are complex enough to produce the benefits needed inside our heart.

Update: Chair in Heart Function Outcomes

In 2016, Dr. Douglas Lee was named Ted Rogers Chair in Heart Function Outcomes. He was tasked with seeking new strategies to improve patient outcomes by exploring data, health systems and individual patient factors and in building new models to reduce rehospitalizations. Importantly, Dr. Lee is not only a clinician-scientist at Peter Munk Cardiac Centre but also heads heart research at the Institute for Clinical Evaluative Sciences (ICES) – where he leverages large administrative databases to carry out population health studies.

This chair, and the diverse collaborations it has sewn, has since proven to be a catalyst in pushing outcomes research forward, beyond the conventional model that's been followed to now. How?

MACHINE LEARNING

We have enabled a far greater focus on machine learning (ML) and data science when it comes to health services. The volume of projects complete, underway, and planned is testing its potential to generate meaningful discoveries. One recent example is a study where we combined ML and expertise in population data to predict cardiovascular outcomes in long-term care residents.

Dr. Lee earned a $1-million strategic innovation grant from the Ted Rogers Centre in 2018, which he credits as the sparkplug to start engaging multidisciplinary experts from the ML space. It has proven central to the work thus far, and in the future ability to analyze data – bringing ideas that seemed far out of reach right into focus. One example: using the language patients when they speak to their clinical care team ("cardio-linguistics") as a way to predict outcomes and rehospitalizations. With ML we can take what patients say, analyze it in depth, and see whether it correlates to hospital admissions in the next 30 days. These are missing links in understanding outcomes that have never before been studied.

EXPLORING THE UNEXPLORED

The chair position has enabled us to visit as-yet unexplored areas in which major questions persist for heart failure outcomes. For example, there is no unified understanding of the interaction between coronary artery disease (CAD) and heart failure. Dr. Lee is leading studies to bring greater clarity to this area with no clear guidelines or evidence-based recommendations.

One of their latest studies on this subject, in 3,000 patients with acute heart failure, found that the use of early angiography is linked to reduced mortality and heart failure hospitalizations. It suggests that angiography is a valuable – and potentially underutilized – tool in diagnosing and managing CAD in acute heart failure. And it is a technique that could be used on an ongoing basis to evaluate whether CAD could be contributing to heart failure exacerbations. Dr. Lee is building a program focused on this very important area to bring clarity to the intersection between CAD and heart failure, how we can improve outcomes, and bring evidence for cardiologists everywhere to consider.

WATERSHED RESEARCH

The chair has spurred interventional research where teams can run trials and use advanced statistical analysis to test hypotheses – which is rare in outcomes research. One landmark example is Dr. Lee's Comparison of Outcomes and Access to Care for Heart Failure (COACH) trial whose results will be released in 2022 and are expected to be widely impactful on how acute heart failure is managed by hospitals and emergency department (ED) physicians.

The world has made few strides in improving outcomes in people with acute heart failure. Most who come to the ED are admitted to hospital and spend a week there. There is no way for physicians to determine those who are at lower-risk of dying and could in fact be discharged home, and high-risk patients who should be admitted. The result is a massive financial cost to the system despite hospitalization not being the right solution for many patients.

Dr. Lee is trying to solve this challenge through COACH, by equipping physicians with novel risk stratification tools to help them move past the "eyeball test" and make precision decisions for each patient. In a sample of 6,000 patients, COACH tested the hypothesis that helping low-risk patients obtain early discharge and receive out-patient care can impact outcomes. Patients themselves helped to design the trial, which leveraged a strong network of heart failure specialists.

The risk stratification is a mathematical model to tell if a patient is high or low risk. At its heart is a world-first EHMRG risk prediction tool that is now proven to work in outperforming doctor decision making for any heart failure patient's risk of dying at seven or 30 days. The basic EHMRG tool is available to the world and actively used not only at UHN but in many major centres, including the Mid America Heart Institute. A more complex algorithm studied in COACH, on the back of positive results, would yield even greater levels of precision care.

COACH is an example of a pragmatic trial, which are the ways of the future in outcomes research. Such trials evaluate a method of care in real-life practice conditions inside hospitals. (One recent pragmatic trial that made waves was from Duke University in 2021, which identified aspirin dosage levels that were best in cardiovascular patients.)

The way COACH was designed and carried out is itself very interesting and its completion will be a landmark moment. If the risk stratification tool has a positive impact on all-cause deaths and heart failure hospitalizations, keeping patients safe and saving the system tremendous money, it will become a major success story for the Ted Rogers Centre for Heart Research.

CHAIR ALLOWS US TO TAKE RISKS – AND UNEARTH NEW FINDINGS

Dr. Lee and his team of collaborators are able, by virtue of this position, to take greater gambles for greater returns – cutting-edge projects that take financing to get off the ground but, because they are experimental in nature, are unlikely to be funded by such bodies as CIHR. One example is being able to link cardiac imaging data from ICES in a bid to uncover patterns and examine how they influence outcomes.

The Chair has been able to tap the Ted Rogers Centre community and open outcomes research into other key fields. These include congenital heart disease, pregnancy and heart disease, cardiotoxicity, childhood heart disease, atrial fibrillation, sudden cardiac death, the use of defibrillators in patients with left ventricular systolic dysfunction, and various surgical and cardiac structural efforts. In this way, this leading effort supported by population health data and machine learning can provide farther reaching answers to many diseases and interventions in the orbit of heart failure. In fact, as it stands, many collaborators are coming to Dr. Lee to explore outcomes components of their work, in Toronto, Hamilton, and other key cardiac centres.

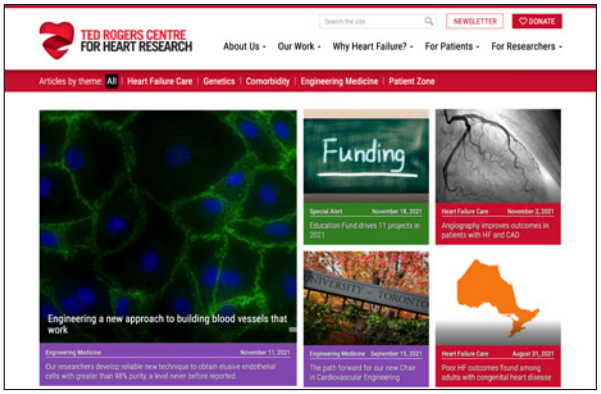
Dr. Lee says that the innovation grant earned by this Chair has opened doors to projects of enormous potential. For instance, he joined 15 principal investigators in leveraging collaborations and emerging knowledge to be shortlisted for a major $3-million Heart and Stroke Heart-Brain grant. This is a key area of the future, understanding the relationship between the heart and brain – for instance, heart failure's impact on cognitive impairment and stroke

Looking ahead, Dr. Lee sees more trials being performed, more uptake of our expert heart failure strategies used across Canada and internationally, and the seedlings of change in we collectively transform heart failure care and the journey of these patients.

Online Metrics: Through Year-6

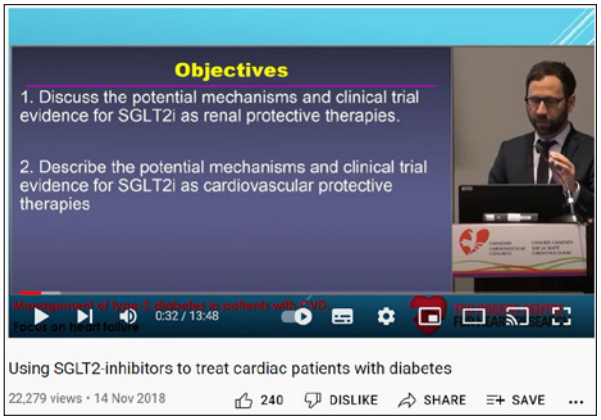
TedRogersResearch.ca

YEAR	USERS	INTERACTIONS WITH SITE
2021	26,196	34,707
2020	19,380	26,151
2019	18,305	24,965



YouTube

709	77,500	22,000
SUBSCRIBERS	VIDEO VIEWS	VIEWS OF TOP VIDEO (RIGHT)



Twitter

1,748	24,780
TOTAL FOLLOWERS	IMPRESSIONS GAINED TOP TWEET (BELOW)



LinkedIn

751
TOTAL FOLLOWERS



Research Productivity: 2015 – 2020

95

RESEARCHERS AT THE TED ROGERS CENTRE FOR HEART RESEARCH PUBLISHED



2,507 PUBLICATIONS

445

TOP JOURNAL (IMPACT FACTOR >10)



777

IMPACT JOURNALS (IMPACT FACTOR 5-10)

2,386

PEER-REVIEWED JOURNAL ARTICLES



116

CONFERENCE PAPERS

5

BOOK CHAPTERS / BOOKS

>4

AVERAGE PAPERS PER RESEARCHER PER YEAR



FIRST OR LAST AUTHOR ON JUST OVER 50% OF PUBLICATIONS

59,312

CITATIONS



10%

OF PUBLICATIONS WERE IN THE



MOST CITED WORLDWIDE

Productivity

MEASURING RESEARCH PRODUCTIVITY AND IMPACT

Common measures of productivity and impact for a research centre include a) the number of publications produced and b) the frequency with which these publications are referenced or cited by other researchers. The following eight metrics, build upon these measures and provide insight into the Centre's productivity and impact over the past four years (2015-2018).

METRICS

a. Number of researchers

The Centre's investigators have grown from 85 to 95, including 33 involved in discovery; 25 involved in personalized medicine and 38 involved in heart failure outcomes.

b. Number of publications

Our researchers published a total of 2,507 publications during the five-year period (2015-2020) or over four papers per researcher per year. Articles, reviews, proceedings papers, books, and book chapters indexed in Clarivate's Web of Science with a Ted Rogers Centre for Heart Research researcher in the author list were included in this count.

c. Number of citations

The Centre's 2,507 publications generated 59,312 citations or over 23 citations per publication on average. This is 1.8x the number of citations of the average paper published globally in the same field and year. Citation metrics are from Clarivate's Web of Science and current as of October 31, 2021.

d. Number of articles in:

i Top journals and

ii Higher impact factor journals

Journal Impact Factor (JIF) is a numerical score based on a journal's citations and has been widely used to assess a journal's impact on the research community. As previously noted, JIF is often used as a proxy for the importance of a journal to its field and can range from a high of 74 to a low of 1-2. As citations are a prerequisite to calculating JIF, new journals where papers have not yet been cited will not have impact factors. In journals classified as Cardiac & Cardiovascular Systems in Clarivate's *SCIE Journal Citation Report*, journals in the top 10th percentile have a JIF > 10 top journals while journals ranked between the 10th and 30th percentile have a JIF of 5-10 higher impact journals.

i. Number of articles in journals with an impact factor >10

Our researchers published 445 articles in journals with an impact factor of greater than 10 during 2015-2020. This represents 18 per cent of our total papers and includes papers in *CA-A Cancer Journals for Clinicians* (IF 508.702); *Nature Reviews Molecular Cell Biology* (IF 94.444); *New England Journal of Medicine* (IF 91.254).

ii. Number of articles in journals with an impact factor of 5-10

Our researchers have published 777 articles in journals with an impact factor between 5 and 10. This represents 31 per cent of our total papers and includes *Cardiovascular Diabetology* (IF 9.951); *Advanced Healthcare Materials* (IF 9.933); *Oncogene* (IF 9.867); and *Chemical Science* (IF 9.825).

e. Cited publications

Of our 2,507 publications, 10 per cent were in the top 10th percentile of the most cited publications world wide.

f. Type of publications

The majority of our 2,507 publications were peer-reviewed journal articles (2,386 or 95 per cent). The remaining publications were conference papers (116) and book chapters/books (5).

g. Senior author publications

In addition, our researchers were either first or last author on 46 per cent of the publications, indicating leadership and or oversight of the related research.



Thank You.